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# VI
# LIVER HOMOTRANSPLANTATION

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Treatment of terminal liver disease by transplantation was founded on the encouragement and knowledge provided by the steadily improving experience in renal transplantation.[17, 27] However, the liver is a far more complicated organ, and its malfunction leads to vastly more complex physiologic derangements. Liver patients are further handicapped, as are heart patients, by the lack of a satisfactory means of artificial support comparable to renal dialysis that could take over the organ's compromised functions during the wait for a suitable donor, or over the critical immediate postoperative period. The transplanted liver must function efficiently practically from the moment of anastomosis or the patient is lost.

Despite these and other difficulties, there has been enough progress in the laboratory and clinic to state that liver transplantation is now a feasible and legitimate, although imperfect, form of therapy, and one that may in certain cases be considered the treatment of choice. Human survivals up to 6 years have been achieved. A great deal has been and is being learned at a pace that suggests that liver transplants will soon have at least as much chance to succeed as kidney grafts now have.

## KINDS OF LIVER TRANSPLANTATION

There are two general approaches to transplantation of the liver. With the first method, the host liver is removed and replaced with a homograft (orthotopic homotransplantation). The alternative technique is the insertion of an extra liver (auxiliary homotransplantation) at an ectopic site. Both procedures were developed in dogs and later studied in other species including rats, pigs, monkeys, and humans. The most encouraging results have been with orthotopic transplantation, for which reason most of this chapter will be concerned primarily with this replacement operation. However, in a special section near the end of the chapter, auxiliary hepatic transplantation also will be briefly considered.

## IMMUNOLOGIC CONSIDERATIONS

### *Is the Liver a Privileged Graft?*

When research in liver transplantation was in its early stages, it was suggested by Cannon[5] that if the liver played a significant role in graft rejection, hepatic homografts might enjoy a better fate than other transplants because presumably the grafted liver would not participate in its own repudiation. The case for this rather mystical view even seemed strengthened by certain experiences with laboratory animals. When immunosuppression in canine recipients was stopped after 4 months, a surprising number of animals continued to thrive either with no signs of rejection or with rejection episodes that waxed and waned remittently.[20, 27] One such dog lived in our laboratory with stable liver function for 11 years and 8 months after transplant. This phenomenon of "graft acceptance" had been noted in dogs with renal transplants,[17, 27] but less frequently.

If the liver thus seemed to be an immunologically favored organ for transplantation in dogs, its status in pigs as observed by Garnier,[9] Terblanche,[29] Calne[4] and in our own laboratory[27] was even more noteworthy. In some experiments with pigs not treated with immunosuppressive agents, identifiable homograft rejection did not occur. In other experiments, rejection was indolent and spontaneously reversed. These surprising results occurred in only a minority of animals. Nevertheless, they had to be attributed to some special privilege of the liver, since porcine skin[11] and kidney grafts[4] were regularly rejected in the usual way.

These observations in both dogs and pigs (and now in other animals) invited certain hypotheses in addition to the one stated above that the new liver helped create an internal milieu favorable to itself. Other possibilities[27] were that the liver was inherently less antigenic than other organs, that its relatively great antigenic mass was a beneficial factor, that its enormous regenerative capacity made it less susceptible than other tissues to the effects of chronic rejection, or, in the view of Calne,[3] that it possessed or released some special factor promoting the induction of specific immunologic tolerance.

Whatever the explanation, overstatement of the case for the liver's privileged status could lead to erroneous conclusions about the practical requirements for immunosuppressive therapy following hepatic transplantation in man. At a research level, another danger could stem from the notion that hepatic transplantation, especially in the pig, is somehow qualitatively unique. The fallacy of such a contention is obvious from the fact that even in the "easy" pig model, the majority of untreated liver recipients died from acute rejection.[27] In dogs and humans, control of hepatic rejection may be difficult or impossible in spite of very heavy immunosuppressive therapy.[20, 27]

### *Rejection Reversal*

Instead of being unique, it is probable that liver homografts vary from other organs only by degree in the host immunologic response they evoke in all species including the pig. In this context, two key observations initially made with kidneys[17, 22] have been extended to the liver,[20, 27] and there is little doubt that

they apply to other tissues as well. The first is the reversibility of rejection. In patients, reversal usually requires intensification of treatment, but it has sometimes been noted without any change in the pre-existing therapy, suggesting that such recoveries had an element of spontaneity. As mentioned earlier, "spontaneous remission" of rejection in the absence of all therapy has been seen both in dogs and in pigs, particularly the latter. The events with the liver in all three species are undoubtedly expressions of the same phenomenon, differing only quantitatively.

### *Graft Acceptance*

The second observation of overriding practical and theoretical interest concerns what has already been referred to as "graft acceptance." In many of the human kidney recipients treated almost a decade ago,[17, 22, 27] it was shown that a melting away of host resistance to the homograft occurred surprisingly early after transplantation, often following an acute rejection crisis. This was manifested by eventual declines in the doses of immunosuppressive agents necessary to retain stable graft function. In many patients, the level of chronic immunosuppression has proved to be less than that which at the outset failed to prevent the onset of a severe rejection.

All treatment has been stopped without subsequent rejection by some of these human renal recipients whom we have now followed for many years, but such a drastic final step is known to be exceptionally dangerous. However, as described earlier, therapy has been successfully discontinued in dogs after kidney transplantation and even more consistently after liver replacement, indicating that graft acceptance may become very complete. In pigs, the barrier of natural host resistance is apparently low enough that the cycle of hepatic graft acceptance can be completed without any immunosuppression at all. Viewed in this way, the curious pig liver experiments become only a special example of, rather than an exception to, a general principle of transplantation. Perper and his associates[13] and subsequently other authors have provided evidence to support both this concept and the original idea that there is a slight but limited biologic advantage in transplanting the liver versus the kidney. Perper showed that a 3-day course of heterologous antilymphocyte globulin (ALG) treatment or other short-term therapeutic maneuvers in pigs permitted long-term acceptance of kidneys in precisely the same way as occurs with the liver in the absence of all iatrogenic intervention.

### *Explanations for Graft Acceptance*

It is indisputable that some element of acceptance of various kinds of grafts occurs often in humans under the appropriate conditions of immunosuppression and that the degree to which this develops is a prime determinant of the long-term prognosis. Unfortunately, the reason for the change in the host-graft relationship is not known. More than one immunologic pathway may be involved.

**Immunologic Tolerance.** Schwartz and Dameshek[16] first suggested the possibility that the continuous presence of a transplanted organ in a host being treated with immunosuppressive therapy could lead to a selective loss of responsiveness to antigens. The suggestion is that specific lymphocyte clones, induced to replicate by the graft antigens, are thereby rendered more vulnerable to the killing effect of immunosuppressive agents than the rest of the lymphocyte population (Fig. 1). Inasmuch as the maintenance of such activated cell lines appears to be thymus-dependent even in adult life, at least in some experimental animals, it is reasonable to be curious about the effect of thymectomy as an adjuvant immunosuppressive measure. The results of thymectomy in a series of our

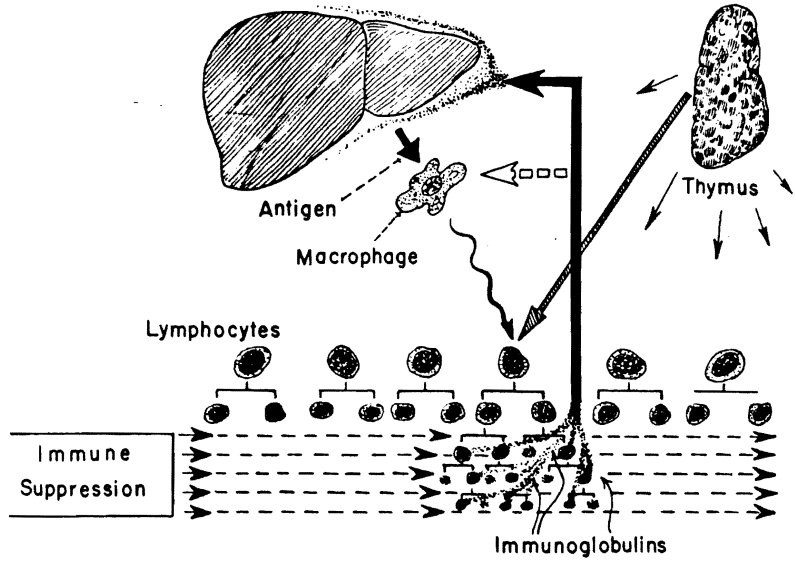


**Figure 1.** Hypothetical mechanims by which nonspecific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone, and hence, tolerance. Since maintenance of such cell lines even in adult life is apparently thymic-dependent in experimental animals, thymectomy would be expected to aid the process; this appears to be true in rodents, but such an effect of thymus removal has not been proved in dogs or humans (see discussion in text). A possible protective role of immunoglobulins elaborated by the replicating cells is also shown.

human renal transplants were inconclusive.[23] While the patients with thymic excision did not have better survival or superior renal function, there were fewer and less severe histopathologic abnormalities when their grafts were examined long after transplantation.

The concept of specific, differential tolerance through "clone stripping" can partly explain the characteristic cycle of rejection and reversal occurring after whole-organ transplantation both in treated animals and man and in the weak and self-resolving crises in the untreated pig. Moreover, it is consistent with the fact that a wide variety of agents that are capable of general immunologic crippling can also provide specificity of action under the stipulated conditions of immunosuppressive treatment during presence of the antigen.

To date, few investigations have been performed in human recipients of chronically functioning renal homografts to establish the presence or absence of classic immunologic tolerance to their donor tissue. It would be interesting to know if skin from these donors would be accepted. One of the reasons why such a test has not been carried out in patients is the potential risk of precipitating an immune reaction that could damage the graft.[12] Of course, viable donor tissue is not available for such an experiment in liver recipients even if this were a desirable undertaking.

Amos and Bach[2] have provided evidence that at least some kidney recipients develop true tolerance to their donors. They performed mixed lymphocyte cultures with peripheral blood from a number of our renal recipients and their donors 2 to 4 years after transplantation. In some cases, the recipient lymphocytes no longer developed blast transformation when exposed to killed donor white cells, although they reacted vigorously to third-party cells. However, in other cases recipient lymphocytes retained their reactivity to donor cells. In experiments, dogs with tolerated kidneys may promptly reject skin or kidney grafts from the original donor.

**Enhancement.** These ambivalent findings do not disprove tolerance through "clone stripping" so much as they suggest that at least another mechanism of graft acceptance may be involved. One such mechanism, termed "enhancement," has been envisioned as a process in which immunoglobulins synthesized by the activated lymphoid tissues circulate to the target tissue and coat it or protect it in some way that is not yet understood (see Fig. 1). Antigraft antibodies, selectively capable of being absorbed by the nucleated cells of the original donor, have been detected in patients carrying well-tolerated renal transplants. Extensive immunoglobulin deposition has been demonstrated by immunofluorescence techniques in long-functioning kidney homografts,[15] but this latter finding usually has an adverse connotation rather than a favorable one.

The two foregoing mechanisms of graft acceptance by tolerance induction and enhancement are not mutually exclusive. The Seattle transplantation group headed by Marchioro, using the techniques developed by the Hellströms, has demonstrated changing host-graft relationships in kidney recipients that are consistent with a multifactorial graft-acceptance hypothesis.[14]

## TISSUE TYPING

Another way by which clinical results might be improved would be effective donor-recipient matching of histocompatibility (HLA) antigens as discussed elsewhere in this chapter. Unfortunately, the state of our knowledge about human histocompatibility systems is still primitive. While a good match between siblings appears to provide a more favorable prognosis after renal transplantation than a poor match, our experience with unrelated subjects provides no such correlation[23] and has led us for the moment to ignore the question of HLA matching altogether in cadaveric cases. In liver transplantation, in which nonrelated cadaveric sources must be utilized exclusively, we have had some excellent results with poor histocompatibility matches and some discouraging results despite close matches.[26, 27] Not only has a correlation with tissue typing been absent with regard to clinical outcome, but no connection at all has been found between the quality of the match and the appearance of the hepatic homograft at subsequent histologic examination.[27] Until the discrimination of the matching methods in nonrelated cases is improved, it is difficult to justify denying a patient an available organ solely on the basis of poor serologic histocompatibility. Nor do we even use most favorable matching as an instrument of selection among candidates for transplantation. At the present time, a more valid criterion may be who has the most pressing need.

There is even reason to believe that screening procedures for preformed antigraft antibodies are not as critical in liver cases as with the kidney.[19] Preformed anti-red cell isoagglutinins that react against donor tissues and cytotoxins that can be detected by their lysis of donor lymphocytes immediately destroy many renal homografts that are transplanted in violation of such positive crossmatches.[17] The liver is very resistant to this so-called hyperacute rejection.[26] In our series, 3 liver transplantations were carried out in spite of red blood group incompatibility and 3 more were performed in confrontation of cytotoxic antibodies. There were no unequivocal hyperacute rejections.

## THE PROCUREMENT OF ORGANS

In contrast to typing, the procurement of a fresh, functioning, nonischemic liver is of paramount advantage and provides the strongest correlation with success or failure.

### *The Source of Donors*

In discussing homograft quality, the technical details of organ preservation become interwoven with, or even distinctly secondary to, ethical considerations about the conditions for the pronouncement of donor death and problems of cooperation by the medical and lay community. Unquestionably, one of the most important advances that have been made in transplantation has been social in nature, consisting of acceptance by the public of the concept of cadaveric organ removal. In turn, this was made possible by a willingness of many members of the medical profession to identify potential donors, to approach family members at a

time of their bereavement, or to indicate in other ways their belief in the propriety of these efforts. By avoiding the glare of lay publicity, this can be and has been done impersonally and with restraint in many areas without exaggeration and without infringing on the personal right to privacy of the individuals involved.

### *Pronouncement of Death*

After the donor has been identified and made available, an effort is made to maintain good liver perfusion up to the last possible moment in order to minimize the ischemic damage that even a short unperfused period may wreak under normothermic conditions. The extraordinary resuscitative efforts required in the donor to prevent circulatory depression in the face of a hopeless prognosis usually require explanation to relatives.

Ultimately, a final decision to discontinue supportive measures may be made after all is in readiness to proceed with the recipient. During the first years of liver transplantation at the University of Colorado, a considerable physiologic penalty was accepted because of criteria that required both brain death and cessation of heartbeat before commencing with organ removal. The price of this insistence was the loss of critical time, and variable ischemic damage both during the agonal stages of circulatory failure and in the minutes after cardiac arrest.[27]

The reason for accepting these conditions was the fear that the quality of terminal care for the donor might be compromised by the pronouncement of death in the presence of a heartbeat. In 1968 our criteria were liberalized in accordance with the concept of irreversible brain injury as it was first outlined and applied at the University of Louvain, Belgium, by Alexandre,[1] and later defended by the Harvard ad hoc committee.[7] Experience since then has convinced us that anxieties about terminal care were unfounded. Acceptance of the brain death concept alleviated one of the most serious problems in liver transplantation, for it virtually eliminated the interval of normothermic ischemic injury and often permitted the organ to be taken in the presence of an intact and effective circulation.

### *Preservation Techniques*

The subsequent preservation of the liver is also of vital importance and has been accomplished by one or more preservation modalities, depending on circumstances, and always including organ hypothermia.[27] With the advantages conferred by the acceptance of brain death, it is often possible to maintain a naturally perfused liver in situ practically up to the moment of its excision. After removal, quick cooling may be accomplished by running a chilled electrolyte solution through the portal vein, thus lowering the donor organ temperature to about 10 or 15° C., which is sufficient for adequate preservation during the hour or so required for the vascular anastomoses in the recipient. In the event of a heart standstill before the recipient is ready, it is possible to employ the procedure used before 1968, when cardiac arrest was required before proceeding; by means of a heart-lung machine, circulation in the cadaver is reinstituted in combination with cooling (Fig. 2). Complicated preservation devices are no longer used.

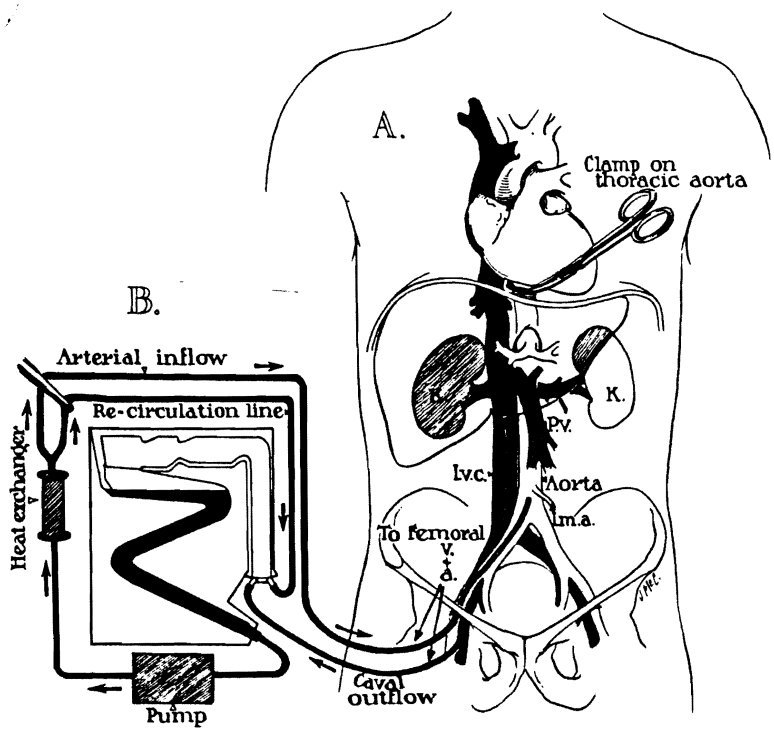


**Figure 2.** Technique of extracorporeal perfusion with a heart-lung machine. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. The extracorporeal circuit is primed with a glucose or electrolyte solution to which procaine and heparin are added. The cadaver is thus anticoagulated with the first surge of the pump. Temperature control is provided by the heat exchanger. Cross-clamping the thoracic aorta limits perfusion to the lower part of the body.

## SURGICAL TECHNIQUES OF ORTHOTOPIC TRANSPLANTATION

### *Species Differences*

The procedure of liver replacement was first accomplished in dogs. The transition from animal experimentation to clinical application required some major technical adjustments and in at least one important and unexpected way demonstrated the need to be alert to the special requirements of human physiology. With removal of the host liver it is necessary to cross-clamp temporarily the great veins draining the intestines (portal vein) and the lower half of the body (inferior vena cava). If provision is not made for decompression of the distal venous pools during the anhepatic phase, dogs either die of shock on the operating table or expire at a later time because of irreparable damage to the mesenteric capillary bed. It was assumed that the same precaution would be necessary in humans and this was accomplished in the first five human recipients by plastic bypasses from the splenic or femoral vein or both to the external jugular veins. There was a dismaying incidence of pulmonary emboli, which caused or contributed to the death of three of the first five recipients. It was suspected either that the clots originated within the bypasses and were actually carried to the lungs during the operation or that they formed a short time later at or near the site where the femoral catheter had been inserted.

The omission of the venous decompression procedure in later patients did not produce any serious or long-lasting circulatory effects, including hypotension. Although a slight duskiness of the intestine developed in some recipients, it immediately disappeared when blood flow was restored through the reconstructed venous channels. One can explain the ease with which portal and vena caval cross-clamping was tolerated by man's inherently richer network of potential collateral channels for the return of blood to the right heart, and by the presumed additional increase in their size and ramifications in consequence of the underlying liver disease.[27] Venous decompression with bypasses has not been used in any recent case.

### *Vascular Anomalies*

In planning a liver transplantation, the surgeon must be prepared for a high incidence of anatomic variations in either the graft or host structures.[27] These have been encountered in almost 40 per cent of our cases. Multiple arteries have been the most frequent anomalies. When these have been in the recipient, most commonly the graft celiac axis has been connected to the host aorta. When the multiplicity has been of the transplant vessels, multiple arterial anastomoses or other variant procedures have been used. There is no question that the need to improvise in these situations imposes an extra risk, particularly in very young recipients whose arteries are quite small and thin-walled even under the best technical circumstances.

### *Bile Duct Problems*

The problems of obtaining adequate bile drainage and avoiding technical errors that may lead to leakage or obstruction may also be complicated by the presence of biliary tract anomalies, and the surgeon must be prepared to tailor his procedure to the individual case.

**Choice of Biliary Drainage.** In several of our first recipients who did not have biliary atresia, bile duct reconstruction was with choledochocholedochostomy over a T-tube stent (Fig. 3*D*). The method lost favor because of a high incidence of biliary fistula, and cholecystoduodenostomy after ligation of the common duct (Fig. 3*A*) became our first choice for a number of years. However, since November, 1973, the preferred technique has been cholecystojejunostomy with a Roux-en-Y loop (Fig. 3*B*), thus removing the homograft from the mainstream of the gastrointestinal tract and draining it through a defunctionalized jejunal limb. Alternatively, Roux-en-Y choledochojejunostomy (Fig. 3*C*) has been used for recently treated patients. In a number of cases it has been necessary to convert from cholecystojejunostomy to choledochojejunostomy (Fig. 3*B* and *C*) because of delayed obstruction at the cystic duct.[19, 26]

**Bile Duct Anomalies.** Ligation of the transplant common duct in conjunction with cholecystoduodenostomy may be dangerous if anomalies are not recognized. Communication between the cystic and common ducts may not always be at the point of their juncture (Fig. 4). In one patient the ducts were externally fused but separated by an internal septum; in 2 others the homograft cystic duct passed behind the common duct and descended for almost 2 inches as one compartment of a double-barreled lumen. In all 3 cases, biliary drainage was inadvertently obstructed when the common duct ligature closed both parallel passages, a technical error that subsequent surgery failed to correct and that proved fatal.

Some of the vascular and ductal anomalies could have been diagnosed preoperatively, resulting either in better planning for surgery or a decision not to operate at all. These earlier cases did not, however, have the benefits of the extensive arteriography and cholangiography that are now used routinely in the donor and sometimes in the recipient as well.

### *Hemorrhage*

Other problems during and after operation may be caused by derangements in the coagulation mechanism that may result in either hemorrhage or thrombosis.[27] As one would expect, acute bleeding can be particularly troublesome during the actual liver transplantation. The very nature of the underlying hepatic pathologic process produces portal hypertension in nearly every patient, and the nature of the operation tends to exaggerate it. The usual consequence is mechanical bleeding that can rapidly assume nightmare proportions during the procedure. Many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are therefore defective in the diseased recipient. These coagulation factors may be even more deficient during the anhepatic phase, or subsequently they may be of dubious quality, depending on the state of preservation of the homograft, on how much ischemia it has suffered, and

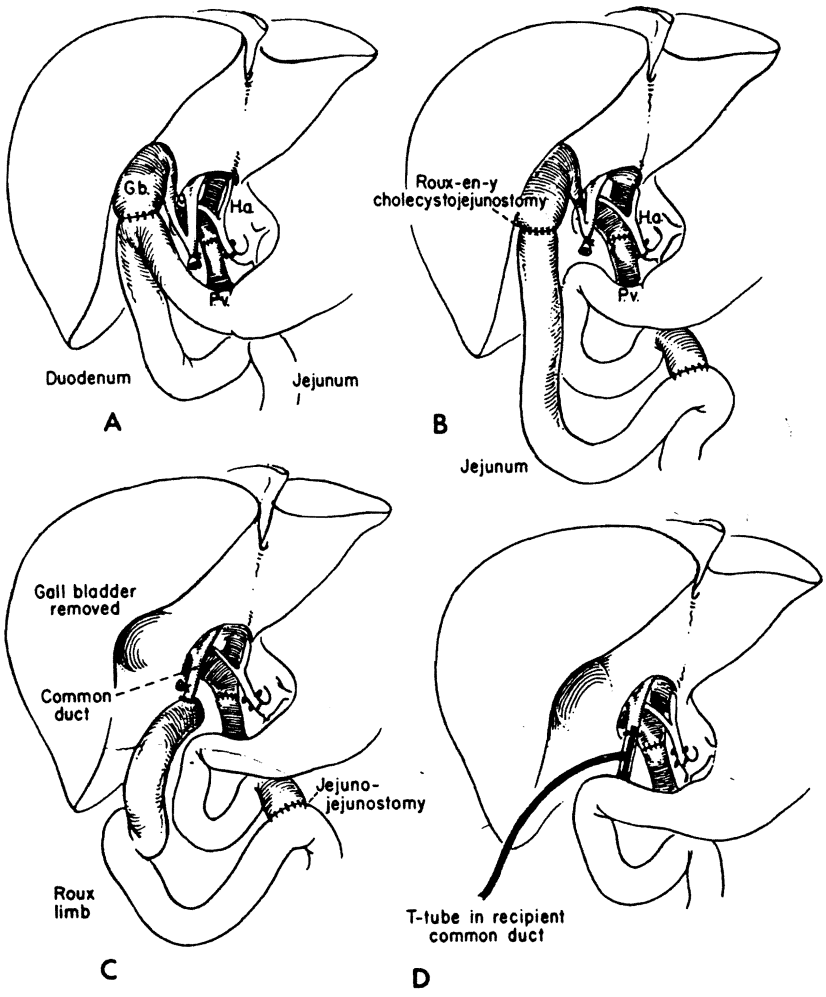


**Figure 3.** Techniques of biliary duct reconstruction used for most liver transplant recipients. *A*, Cholecystoduodenostomy. *B*, Cholecystojejunostomy. *C*, Choledochojejunostomy after removal of gallbladder. *D*, Choledochodochostomy. Note that T-tube is placed if possible in recipient common duct. (From Starzl, T. E., et al.: Surg. Gynecol. Obstet., *142*:487, 1976.)

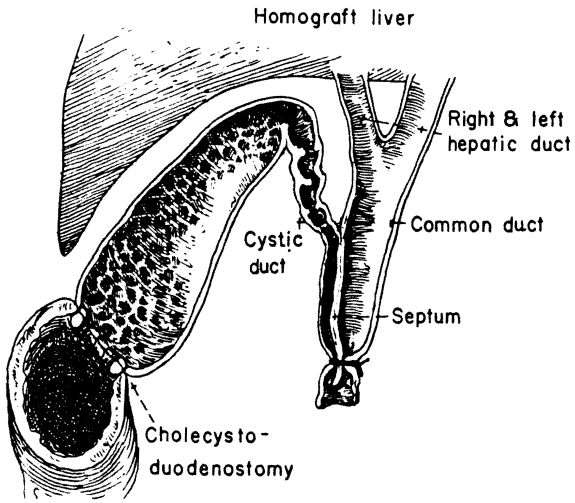


**Figure 4.** The anatomic basis for a technical error which cost the life of a patient. Distal ligation of the double-barreled extrahepatic duct system resulted in total biliary obstruction.

on how much immediate functional capability it has retained.

When hemorrhage occurs, the surgeon's challenge is to use any and all available hemostatic tactics—ligating, suturing, cauterizing—until the revascularized homograft can participate in what is hoped will be appropriate coagulation function. With our earlier patients, whose homografts were generally of less than optimal quality for the reasons stated earlier, an attempt was made to treat bleeding problems by administering thrombogenic agents. However, hypercoagulability was caused in some instances. The unacceptable incidence of pulmonary embolism in these patients led us to abandon this approach.

In retrospect, it is possible that the coagulability induced by exogenous thrombogenic agents might be prohibitively additive to the clotting brought about by the homograft which, when it begins to function, may overreact. Indeed, the better the condition of the transplant, the greater the risk of unwanted coagulation. Almost every series of liver transplants, including our own, has at least one example of thrombosis of

the hepatic arterial circulation to which a rebound phenomenon may have contributed. The use of anticoagulants to forestall this emergency is dangerous. Documented intravascular clotting during the operation would be an indication for heparin, but such proof is hard to obtain. Moreover, heparinization is a double-edged maneuver; depressed clotting can have devastating effects on patients submitted to such major trauma and with so many potential bleeding sites.

In general, it is now considered best to avoid iatrogenic manipulation of the clotting process with either thrombogenic or anticoagulant agents. Instead, our current approach is to leave correction of coagulation abnormalities to natural processes, intervening only under special circumstances and for very specific indications.

### *Anesthesia*

During operation, there are other metabolic abnormalities than those concerned with coagulation. These contribute to the complexity of anesthetic management. Not only is the procedure long and difficult, but even more important, it is an operation on the primary organ involved in the metabolism and detoxification of most common anesthetics. At any point during the operation, the liver is either inherently impaired, absent, or untried in its new setting. Hence, the task of the anesthesiologist is to administer correctly drugs that, first, are not hepatotoxic and, second, do not depend primarily on the liver for their degradation. In our cases, reliance has been placed mainly on combinations of volatile agents in nonexplosive concentrations. Such management permits use of the electrocautery, gives flexibility in lightening or deepening anesthesia, and allows anesthesia to be abruptly stopped if required by changing physiologic circumstances.[27]

### *Other Operative Problems*

The foregoing are some selected difficulties associated with liver transplantation. There is a long list of other technical pitfalls: adrenal venous infarction, air embolism, and crushing of the right phrenic nerve by too high a clamp on the upper vena caval cuff, to mention but a few. The reader interested in a more detailed discussion of these and other surgical problems is referred to more detailed publications.[19, 26, 27] These technical matters have played a major role in the mortality encountered in our first cases. Even though deaths from such causes are theoretically avoidable, technical misadventures still constitute the leading cause of failure, as has been very well documented in our exhaustive study of the first 93 consecutive cases.[26]

## IMMUNOSUPPRESSION

The immunosuppressive therapy in liver transplantation has borrowed heavily from the experience gained with human renal transplants. Two general treatment programs were evolved with the simpler kidney model and then applied to the liver recipients.

### *Double Drug Therapy*

The first protocol, which was used from 1962 to 1966 for all organ recipients at the University of Colorado, consisted of "double drug" treatment with azathioprine and the synthetic adrenal cortical steroid, prednisone.[17] Evolution of the use of these two agents together, appreciation of their marked synergism, and demonstration that rejection could be readily reversed by increasing the steroid doses were among the advances that made clinical transplantation practical and that introduced what is known as the modern era of this field. But in spite of fair results with renal transplantation, the double drug therapy either did not prevent rejection of hepatic homografts or else it proved too toxic to permit host survival. Six patients treated with liver transplantation from 1963 to 1965 died in a month or less.

### *Triple Drug Therapy Including ALG*

In 1966, heterologous antilymphocyte serum (ALG) was introduced clinically at our center as a third immunosuppressive agent, added to the drugs mentioned above.[24, 27] Since then, this triple drug therapy has been given to all our renal, hepatic, and cardiac recipients, even though not all transplant surgeons concede the need for ALG.

Almost all of our human liver recipients who achieved chronic survival were treated with the combination of azathioprine, prednisone, and intramuscular ALG. In the event of a rejection episode, it is the steroid component that has proved to be the agent most amenable to quick adjustment of dosage according to need. In the event that hepatotoxicity of azathioprine is suspected, we have been free to substitute the alkylating agent, cyclophosphamide, which has immunosuppressive qualities equivalent to azathioprine.[28]

### *Penalties of Immunosuppression*

Some of the hypotheses of the actions of these immunosuppressive drugs have been discussed elsewhere[27] and reviewed earlier in this chapter. Suffice it to say, as was emphasized at the outset of this chapter, the method by which these agents are used in conjunction with the actual transplantation may conspire to permit selective abrogation of the host rejection response. If this were not true, there would be little hope of rehabilitating patients and returning them to life in an unrestricted environment, since each of the individual agents can cause general immunologic crippling more or less in proportion to the dose used.

**Risks with All Organs.** The most obvious penalty of a depressed immune system is heightened susceptibility to infection.[17, 27] However, it has also become obvious that chronically immunosuppressed patients have an increased vulnerability to de novo malignancies.[17, 27] In our own series of chronic survivors after renal transplantation, more than 5 per cent have developed either mesenchymal or epithelial malignant tumors. Almost all other major transplantation centers have recorded this complication, which is presumably due

to failure of the depressed immunologic surveillance mechanism to identify the tumor tissues as alien and to eliminate them or restrict their growth.

**Extra Risks for Liver Recipients.** In addition to the foregoing general liabilities of immunosuppression, there are some special risks for the liver candidate. One is the fact that hepatic injury in all kinds of organ recipients has commonly been produced by the agents, individually or in combination, of the therapeutic regimen.[27] In some instances, virus hepatitis, apparently made chronic by the partial immunologic invalidism of the host, has been a plausible explanation. In others, hepatotoxicity of the drugs was probably responsible. With liver malfunction, dose control of some of the agents may become difficult, since the liver participates in their pathways of action or degradation. These hepatic factors are obviously important in any situation requiring immunosuppression, but they have heightened significance for a traumatized liver transplanted to a new and hostile environment.

It was mentioned in the preceding section that infection was a major risk to any immunosuppressed patient. In the liver recipient, postoperative sepsis of the graft itself has proved to be a special problem, without doubt partly because of the anatomic location of the orthotopically placed organ, interposed between the intestinal tract and the heart. Bacteria from the bowel, particularly of the gram-negative variety, can be brought into contact with the transplanted liver via the intestinal veins draining into the portal vein or, far more importantly, by retrograde spread up the duct system after passage through the biliary anastomosis (Fig. 5). In either event, the presence of nonviable hepatic tissue provides a perfect medium for bacterial growth. Eventually, partial gangrene of the transplant can result, with characteristic nonvisualizing areas on the liver scans (Fig. 6), gram-negative bacteremia, and all the findings of generalized sepsis.

**Avoidance of Homograft Sepsis.** Early in our clinical series, the above findings of graft and systemic infection led us to consider the essential problem to be one of bacterial invasion and thus prompted reductions of immunosuppression. Such decisions were tragically incorrect and were followed by necrosis and infection of large parenchymal areas. Experience soon taught that ischemia of portions of the liver was the initiat-

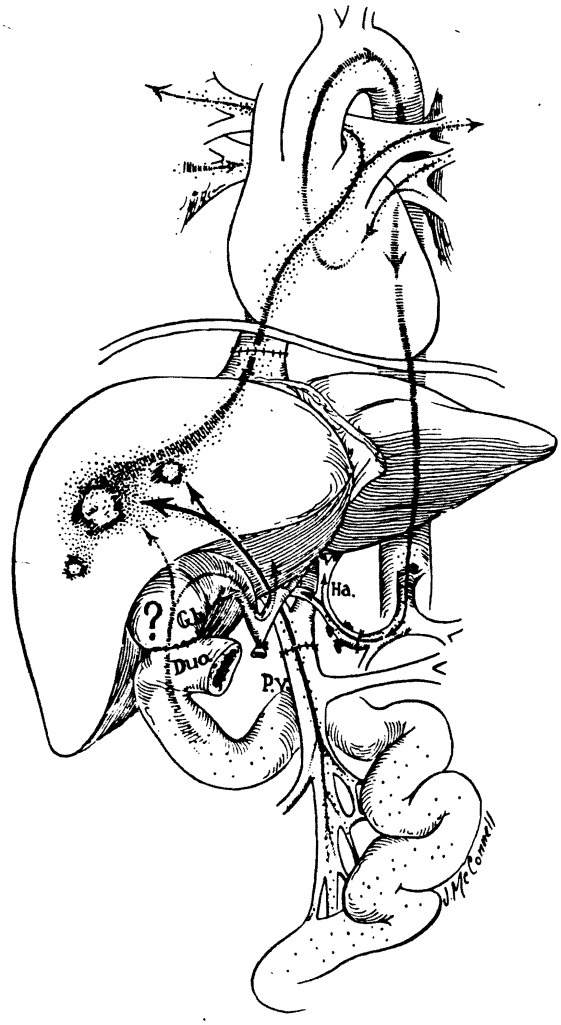


**Figure 5.** An explanation of the predisposition of the liver to bacterial sepsis. Presumably the invading microorganisms enter via the portal vein or through the reconstructed biliary tract. (From Starzl, T. E., et al.: Ann. Surg., *168*:392, 1968.)

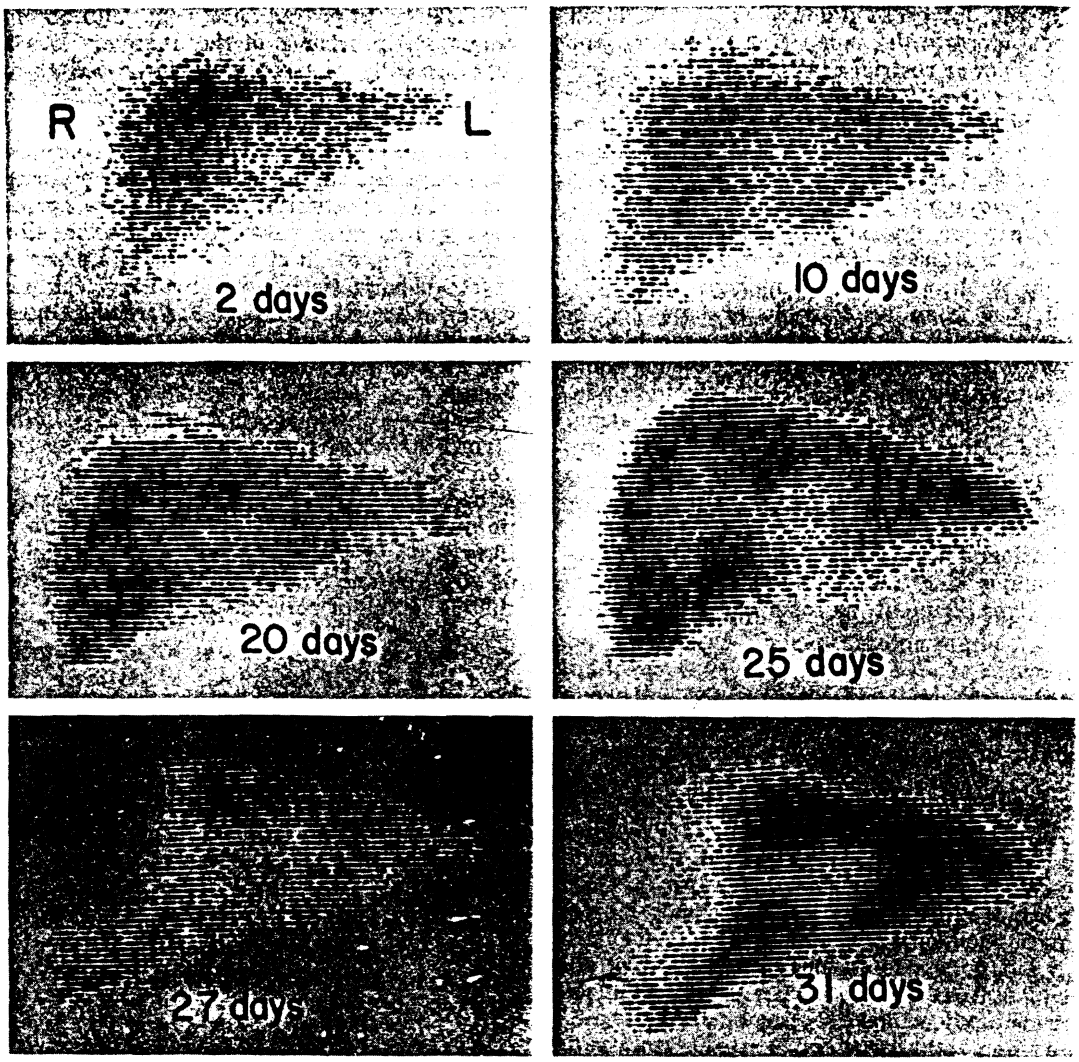


**Figure 6.** Postoperative technetium scans of the liver in a 13-month-old infant whose indication for orthotopic transplantation was biliary atresia. *2 days:* The small homograft is normal. *10 days:* An increase in size is evident although the general configuration of the organ is still normal. *20 days:* No further change is noted. *25 days:* The examination was conducted as an emergency when gram-negative septicemia developed and very high increases in the transaminases appeared. Areas of decreased isotope uptake are obvious in the right lobe and the central part of the liver. *27 days:* A striking extension of the process can be seen less than 48 hours later. A débridement procedure was carried out the same evening. *31 days:* Four days after débridement the radiographic appearance was improved.

ing event, and that the basis for the ischemia was rejection.[27] Consequently, immunosuppression should ordinarily be increased rather than reduced if this complication is thought to be impending. When this was done by giving substantially higher doses of prednisone (as noted, the only highly dose-maneuverable component of the immunosuppressive triad), the incidence of regional hepatic gangrene fell to nearly zero. It should be added that our prophylactic treatment protocol includes heavy antibiotic treatment for the first postoperative week, including agents effective against gram-negative bacteria, after which this therapy is stopped.

The other vitally important step in reducing homograft sepsis has been to use biliary reconstructive techniques that prevent systematic contamination by gastrointestinal contents (see Fig. 3*B*, *C*, and *D*).

## INDICATIONS FOR LIVER REPLACEMENT

The understanding of regional hepatic gangrene that evolved illustrates well the learning process of caring for patients receiving a new kind of treatment. With the acquisition of experience, other important issues have also been clarified, including that of the indications for liver replacement. A brief summary of our first 93 consecutive recipients, treated from March, 1963, to November, 1974, can be used to illustrate these indications in the light of the results after

a minimal potential follow-up of 14 months.[26] The 93 patients were aged 3 months to 68 years.

### Hepatic Malignancy

The indication for 15 of these transplants was hepatoma, cholangiocarcinoma, intrahepatic duct cell carcinoma, or hemangioendothelial sarcoma. Seven of these patients died within 39 days from technical problems of one kind or other.

Six patients had more prolonged survival, but died after 76, 87, 143, 339, 400, and 432 days. In all 6, metastases were present and in 5, the recurrences were directly responsible for death. Two other more recently treated patients who had intrahepatic duct cell carcinomas are still alive after 22 and 16 months, but the recipient with the longer follow-up has extensive metastatic disease.

An additional unsuspected hepatoma was found in a 4-year-old child treated for extrahepatic biliary atresia. This child is still alive, now 6 years after the operation; she has no evidence of recurrence of neoplasia.

Because of the high rate of recurrent malignancy, it has become our policy to consider liver replacement for primary liver tumors only under the most exceptional circumstances, even though our experience and that of Daloze of Montreal and Calne of Cambridge have demonstrated the possibility of an occasional tumor cure.

### Biliary Atresia

Far more desirable candidates are those without neoplasms, in spite of the fact that the technical difficulties in benign hepatic disease are more severe because the patients tend to be sicker and to have more advanced portal hypertension. Moreover, if the diagnosis is biliary atresia, an increased incidence of vascular anomalies can be expected to compound the difficulties, together with the small size of the structures to be anastomosed in these young patients.[27] Nevertheless, the longest survivors of liver transplantation in the world are those who had this disorder (Fig. 7). Of our own series of 40 patients with biliary atresia, treated 14 months or longer ago, including the child with the incidental hepatoma already mentioned, 11 lived for longer than 1 year and 7 are still surviving with completely normal liver function 16 months to 6 years after operation. Three of the late deaths after 13, 13½, and 30 months were from recurrent hepatic insufficiency caused in two instances by chronic rejection, but probably in the third by indolent viral hepatitis. The fourth late death after 41 months occurred a few weeks after a bout of Hemophilus septicemia, which had resulted in multiple organ damage.

The potential of liver transplantation for the treatment of biliary atresia will not be realized until the heavy early mortality is reduced. A recent analysis of the deaths within the first postoperative year has

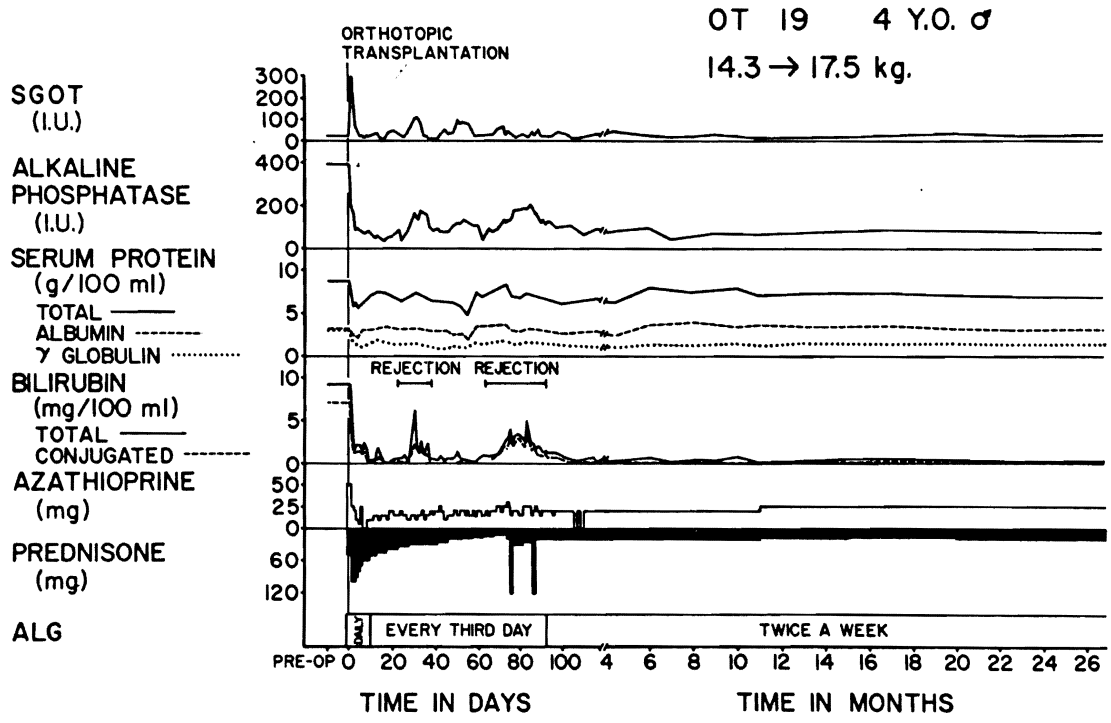


**Figure 7.** The course of a 4-year-old child after orthotopic liver transplantation for the indication of biliary atresia. Note the rejection episodes at 1 month and 2½ months, which were easily controlled. The patient, who died after 3½ years, was for a long time the longest-surviving liver recipient in the world. This distinction now belongs to another child whose original disease was biliary atresia and who has been followed for 6 years after transplantation.

shown the overwhelming contribution of technical and mechanical problems to the acute loss rate.[26] Inability to control rejection played a surprisingly minor role. With the use of microsurgical techniques and an increased alertness to biliary tract complications, there is no reason why these children should not be the best of all potential candidates for liver replacement.

### *Cirrhosis*

Among the 93 consecutive patients treated with liver replacement, there were 18 with cirrhosis due to chronic aggressive hepatitis (9 children and 9 adults) and 9 with end-stage alcoholic cirrhosis. Six of the 18 patients with chronic aggressive hepatitis lived for at least 1 year. Only 1 of the 9 with alcoholic cirrhosis lived into the second postoperative year.

Undoubtedly, one reason for the bad experience with cirrhotic patients has been a reluctance to recommend such therapy except in the agonal stages of the disease. Now that the feasibility of long-term survival and rehabilitation has been demonstrated, transplantation at an earlier time probably should be considered, particularly in cases of postnecrotic cirrhosis in which the maximal value of medical management and of abstinence from alcohol has already been realized.

### *Other Indications*

Periodic reassessment of the influence of the original host disease upon the outcome will also be necessary insofar as this factor influences future case selection. None of the diseases for which liver transplantation has been used so far can be categorically precluded as an indication for further trials, especially in children. The brightest chapter in liver transplantation has been in the treatment of inborn errors of metabolism in children, including our two cases of Wilson's disease (one patient is alive after 5 years, the other died after 6 years [Fig. 8]), our patient with alpha-1-antitrypsin deficiency (alive after 2¼ years), and Daloze's child with Niemann-Pick disease,[6] who is alive after 1½ years. It has become clear that the hepatic-based inborn errors of metabolism are all potentially curable with liver transplantation.

Other conditions for which transplantation has been performed include congenital biliary cirrhosis, primary biliary cirrhosis, secondary biliary cirrhosis, sclerosing cholangitis, the Budd-Chiari syndrome, and acute and chronic serum hepatitis due to the $HB_sAg$ virus.

Even continued efforts to treat recipients with chronic $HB_sAg$ antigenemia are probably warranted, especially if hyperimmune specific gamma globulin therapy can be offered. Without such treatment, it seems highly probable that the new liver will eventually be afflicted with the same disease that destroyed the native organ (Fig. 9).

### *Future Prospects*

In a positive sense, the most important conclusion that has emerged from the experience with our first 93

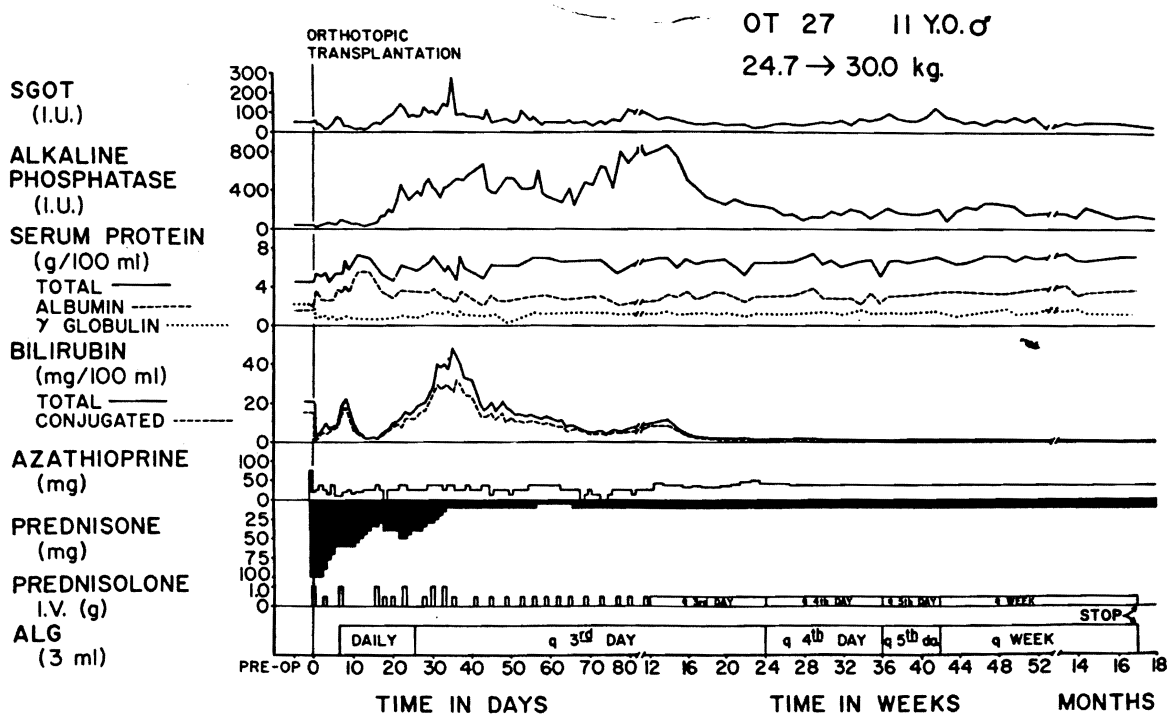


**Figure 8.** Course of a child with Wilson's disease and hepatic cirrhosis who was treated with liver replacement in July, 1969. He lived for six years without stigmata of recurrent Wilson's disease. Eventually his death was caused by chronic partial biliary duct obstruction of the homograft, which led to widespread intrahepatic sludge formation. (From DuBois, R. S., et al.: Lancet, *1*:505, 1971.)

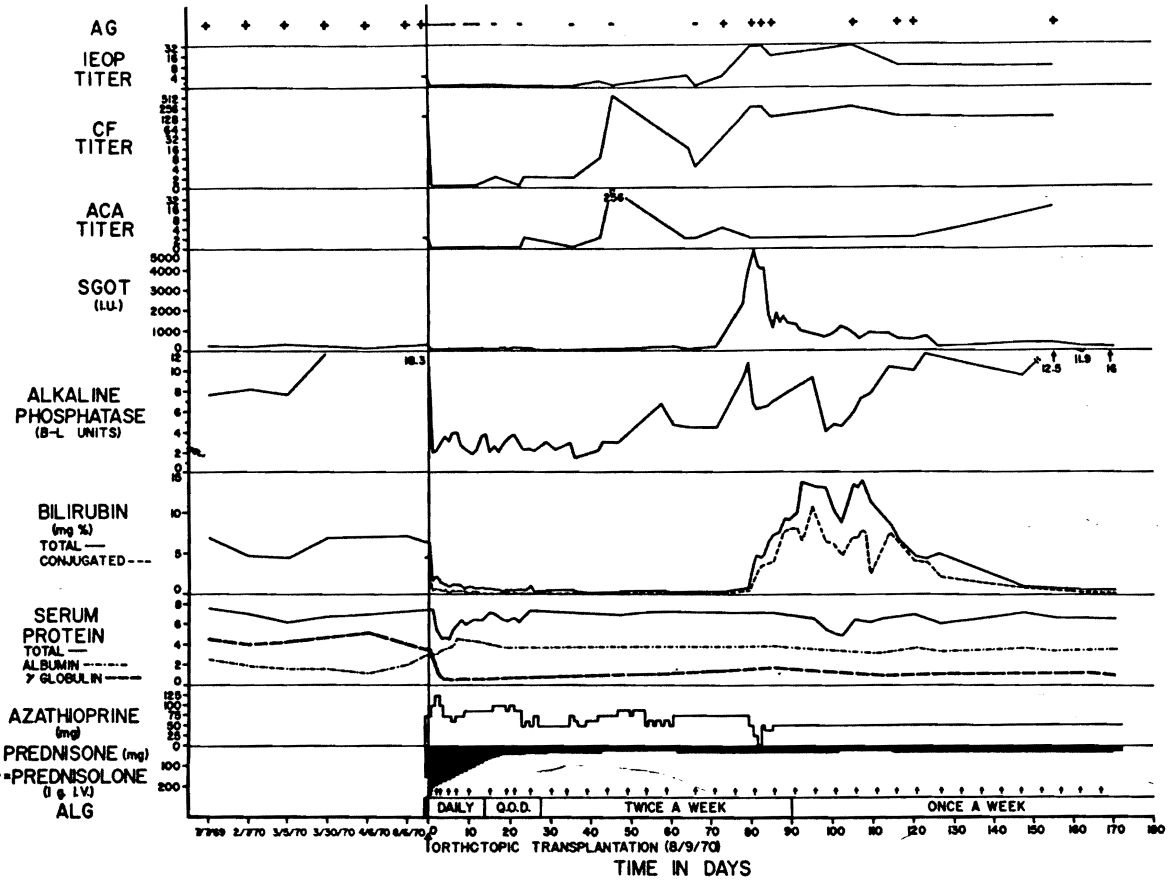


**Figure 9.** The course of a patient who was terminally ill with chronic aggressive hepatitis, Australia (Au) antigen-positive. She was treated by liver replacement. Note that all serologic evidence of serum hepatitis disappeared immediately after operation only to return some weeks later. AG, agarose gel micro-Ouchterlony test for Au antigen. IEOP, quantitative immunoelectro-osmophoresis test for Au antigen. CF, complement fixation test for Au antigen. ACA, anticomplementary activity, which is thought to reflect the presence of circulating antigen-antibody complexes; the test is not immunologically specific for Au antigen. Normal Bessey-Lowry (B-L) units for alkaline phosphatase are less than 3. This patient eventually developed a modified serum hepatitis in her homograft and died 20 months after transplantation. (From Torisu, M., et al.: Ann. Surg., *174*:620, 1971.)

consecutive liver replacements was that prolonged survival repeatedly was possible. A total of 27 patients lived for at least a year following operation, and 16 of this group are still alive after more than 1 to almost 6 years. The outlook has slowly improved, although not to a satisfactory state. The first 25 recipients who formed the basis of a monograph on liver transplantation[27] included only 5 one-year survivors. The next group of 25 contained 6, and the group from 51 to 75 had 8 one-year survivors. There have already been 8 one-year survivors among the 18 patients beginning with number 76.

The chronic survivors, particularly those in recent times, have had remarkably stable liver function, and usually they have achieved complete social rehabilitation. Survival of more than a year after orthotopic liver transplantation has been recorded from other centers by Williams and Calne and their associates in England,[30] by Daloze and his colleagues in Canada,[6] and by Hume and his associates in the United States.[10]

In our own case material of 93 consecutive cases,[26] rejection of the liver as judged by classical histopathologic criteria played a surprisingly small role in the heavy overall mortality, accounting for less than 10 per cent of the deaths. Technical or mechanical problems, especially those of biliary duct reconstruction, were a far greater cause of failure, as were systemic infections. When abnormalities of liver function developed in the postoperative period, the nearly automatic diagnosis of homograft rejection proved in retrospect to have been wrong in most instances.

Further development of liver transplantation depends upon three kinds of progress. First, earlier decisions for transplantation will be necessary, especially in adult recipients. Second, there must be reduction of operative and early postoperative accidents and complications by more discriminating case selection, purely technical improvement, and better standardization of biliary duct reconstruction. The third area will be sharpening the criteria for the differential diagnosis of postoperative hepatic malfunction, includ-

ing the liberal use of transhepatic cholangiography and needle biopsy. Only then can better decisions be made about changes in medication or about the need for secondary corrective surgical procedures.

The frequency with which liver transplantation is being used is steadily increasing. Within the next five years, it is virtually certain that this approach to the treatment of liver disease will become far more widely accepted.

## AUXILIARY LIVER TRANSPLANTATION

Both in experimental animals and in patients, survival after auxiliary transplantation has been inferior to that with the orthotopic procedure. The reasons for these disappointing results have not been entirely clear, but plausible explanations have been advanced indicting both metabolic and mechanical factors.

### *Metabolic Considerations*

When auxiliary liver transplantation was first attempted in immunosuppressed canine recipients, a curious and disquieting observation was soon made.[21] The extra organs underwent rapid shrinkage, which was usually evident within 2 weeks and which was very advanced at all times after one month. Subsequent research has shown that the atrophy can be prevented if the homograft's portal inflow is provided with blood returning from the pancreas. The most important constituent of portal venous blood in maintaining liver health has been demonstrated unequivocally to be insulin.[18, 25]

### *Clinical Experience*

In most of the early attempts at auxiliary liver transplantation, the homograft was not given an acceptable blood supply by the criteria just described. The results were uniformly poor.[27]

More recently, Fortner[8] has reported survival of more than one year in a child with biliary atresia whose auxiliary liver was furnished with both an arterial and an adequate splanchnic venous inflow similar to that shown in Figure 10.

This single success has demonstrated the feasibility of auxiliary liver transplantation. However, the technical difficulties of achieving optimal revascularization, the abdominal over-crowding by the addition of an extra large organ, and the consequent pulmonary complications that have plagued auxiliary transplant recipients have all suggested that the auxiliary procedure will play no more than a minor role in the exploitation of clinical liver transplantation.

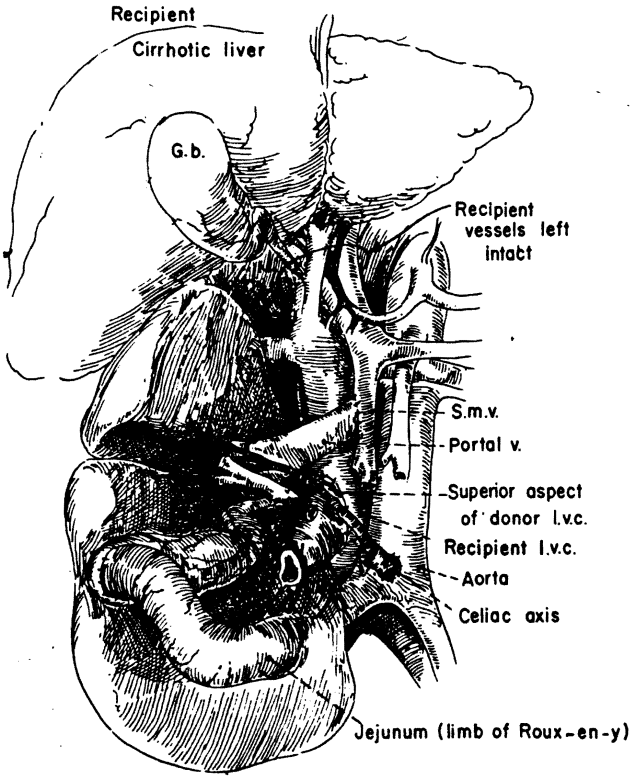


**Figure 10.** Auxiliary liver transplantation with a technique that provides an adequate blood supply for the homograft. Note that the transplant is given a double blood supply and that the venous component is from the nonhepatic splanchnic bed. Biliary drainage can be with a Roux-en-Y cholecystojejunostomy.

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*The article contains a clinical-pathologic analysis of the first 93 consecutive cases of orthotopic liver transplantation carried out at the University of Colorado, with a minimum potential follow-up of 14 months. Emphasis was on the causes of failure and upon means of improving future results.*

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# VII

# LUNG TRANSPLANTATION

*Keith Reemtsma, M.D., and Henry M. Spotnitz, M.D.*

## HISTORICAL ASPECTS

Among the various organs, the lung was one of the last to be used in experimental transplantation. Demikhov[17] first investigated experimental pulmonary transplantation extensively. He developed techniques for transplantation of lobes and the intact lung in dogs. Metras[40] was the first to utilize the atrial cuff technique for the venous anastomosis. Juvenelle in 1951 performed the first successful orthotopic auto-